REMARKS

Claims 1, 14, 24, 25, 26, 28-31, and 36-51 were pending in the application. Claims 1, 14, 24-26, 28-31, 36 and 37 have been canceled without prejudice and new claims 52-58 have been added. Claims 38-51 have been amended. Accordingly, claims 38-58 are currently pending in the application. Support for the new claims can be found in the application and claims as filed and/or as previously pending. Specifically, support for the phrase "over a length of at least about 10 amino acids" and "at least about 30-40 amino acids" can be found at least at page 11 of the published application. Support for the phrase "immunogenic amino acid sequence" can be found at least at page 20, line 27 of the published application.

No new matter has been added.

Restriction Requirement

The Examiner required restriction among inventions I- XI. Applicants argued that the restriction requirement set forth in the action of September 6, 2002 was improper because i) no objection as to lack of unity of invention was raised during the international phase of the application and it is improper under the PCT for national offices to require compliance with the requirements relating to the form or contents of the application different from or additional to those which are provided for in the PCT (Art 27 PCT) and ii) an allowable generic linking claim is present in the application.

Applicants also argued that Rule 13 of the PCT provides that a group of inventions linked by special technical features (which define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art) shall be examined in an international application. Accordingly, multiple products and methods, linked by special technical features,

are proper. The pending claims are all based on the special technical feature that hepatitis C virus produces polypeptides are encoded in their entirety, or in part, in alternate reading frames, e.g., +1 and +2 to the standard open reading frame. ***As set forth in more detail below, this special technical feature is novel and unobvious over the art cited by the Examiner.***

Moreover, Applicants presented an allowable generic claim, claim 31 (now replaced by claim 52) which is generic to claims 28 and 29 (now replaced by claims 53 and 54). Claim 52 is drawn to methods of diagnosing HCV infection, comprising detecting a molecule indicative of an infection with hepatitis C virus (HCV) wherein the molecule is selected from the group consisting of: i) a polypeptide comprising an immunogenic amino acid sequence of an HCV alternate reading frame polypeptide, ii) a polypeptide comprising an amino acid sequence of an HCV alternate reading frame polypeptide that is immunoreactive with an antibody that specifically binds to an HCV alternate reading frame polypeptide, and iii) an antibody that specifically binds to an HCV alternate reading frame polypeptide. Claim 52 embraces the species of detecting polypeptides comprising alternate reading frame sequences (claim 53) or antibodies that bind to such polypeptides (claim 54).

According to linking claim practice set forth in MPEP §§ 809 and 809.03, it is Applicants understanding that the linking claim (claim 52) will be examined with the invention elected and should the claim be allowed, the restriction requirement will be withdrawn. Applicants understand that the claims are currently being examined to the extent that they read on detection of HCV alternate reading frame polypeptides.

Withdrawal of Certain Rejections

Applicants gratefully acknowledge the withdrawal of the rejection of claim 29 under 35 U.S.C. §112, first paragraph.

Rejection of claims 29, 36, 31, 38-41 Under 35 USC § 103(a).

Claims 29, 36, 31, 38-44, and 46-49 have been rejected under 35 USC § 103(a) as being unpatentable over either of Lo et al. (Virology 199:124-131, 1994; Ref B1) or Lo et al. (Virology 213:455-561, 1995; Ref B2) in light of Xu et al. 2001 (The EMBO Journal 20(14):3840-3848). Claims 1, 14, 24-26, 28-31, 36 and 37 have been canceled. This rejection is respectfully traversed to the extent that it may be applied to any of the presently pending claims.

The Examiner states that "[w]hile neither Lo B1 nor Lo B2 discloses the P16 [peptide] as being an HCV +1 reading frame polypeptide, both disclose it as a protein of interest in HCV infection and both disclose detecting it an immunoassay." The Examiner further states that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to have detected the HCV P16 of Lo B1 or Lo B2 in the body fluid or tissue of a subject by immunoassay and to correlate the presence of HCV P16 with the presence of HCV infection because both Lo B1 and Lo B2 disclose the HCV P16 as a polypeptide that is specifically associated with the expression of HCV core nucleotide sequence."

The Examiner also relies on the teachings of Xu et al. (2001) as providing evidence that the prior art HCV protein P16 of Lo et al. is an HCV +1 protein. However, as set forth in more detail below, the P16 protein taught by Lo (B1 and B2) and the P17 (F protein) taught by Xu et al. (2001) have different characteristics and, since the Xu reference was published in 2001, it is not available as prior art nor can it be used to provide the motivation to modify the teachings of the primary references.

To establish a *prima facie* case of obviousness for the claimed invention, there must have been some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to

combine reference teachings in the manner proposed by the Examiner. Second, there must have been a reasonable expectation of success at the time the invention was made. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See M.P.E.P. 2143. The prior art must suggest "to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process" and "[b]oth the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.* 837 F.2d 469. 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

The pending claims are directed to methods of diagnosing HCV infection, comprising detecting a molecule indicative of an infection with hepatitis C virus (HCV) wherein the molecule is selected from the group consisting of: i) a polypeptide comprising an immunogenic amino acid sequence of an HCV alternate reading frame polypeptide, ii) a polypeptide comprising an amino acid sequence of an HCV alternate reading frame polypeptide that is immunoreactive with an antibody that specifically binds to an HCV alternate reading frame polypeptide, and iii) an antibody that specifically binds to an HCV alternate reading frame polypeptide. Such polypeptides and their use in diagnostic assays are not taught or suggested by the art of record.

The Lo B1 reference fails to teach or suggest the class of HCV alternative reading frame polypeptides presently being claimed. The authors of Lo B1 identify a polypeptide smaller than P21 core, P16. The reference teaches that P16 is an HCV core gene product that is initiated from the initiation codon of the full length core protein, p21 (see page 128, column 1), and it contains no suggestion that P16 contains any segments that are not part of the core protein. The Lo B1 reference teaches that P16 is a shortened form of the core protein, ***not a polypeptide that contains regions encoded in an alternate reading frame***. The reference also teaches that P16 is

recognized by antibody against the core protein (see page 126, column 2, paragraph 1). The reference does not contain any suggestion that P16 would be expected to react with antibodies directed against epitopes encoded in an alternate reading frame, nor does it contain any suggestion that P16 would stimulate the production of such antibodies, nor does it contain any suggestion that the production of P16 indicates that polypeptides containing epitopes encoded in alternate reading frames are produced during natural HCV infections (whether these infections would be stimulated by the HCV-1 variant, or any other variant). In addition, the reference teaches that P16 accounts for virtually 100% of the polypeptide produced by in vitro translation of HCV-1 RNA transcripts incubated in rabbit reticulocyte lysates (see Figure 4). The reference provides only two mechanisms to account for P16 synthesis, stating that "it could be synthesized due to premature termination of translation or produced through proteolytic cleavage of the nascent polypeptide chain during translation." ***Thus, Lo B1 teaches that P16 is a shortened form of the core protein.***

The Lo B2 reference confirms the teaching of Lo B1 and states that P16 and P21 are co-amino-terminal (see page 459, column 1, paragraph 2). The amino terminal sequence of P16 is taught to be: XTNPKPQK$_9$KNKRNTN, identical to the P21 sequence (see Table 1). According to this teaching, p16 is encoded by the standard HCV reading frame which specifies the core protein and, therefore, is not an alternate reading frame polypeptide. The reference also examines expression of plasmids comprising HCV core protein sequence in the presence or absence of its downstream E1 envelope protein sequence and teaches that P16 is the major core protein product when the HCV-1 core gene is expressed in the absence of its down-stream E1 envelope protein (see page 460, column 1, paragraph 4). In addition, the reference teaches that P16 is expressed in the nucleus of cells (see page 456, column 1, paragraph 2).

In summary, the Lo B1 and Lo B2 references teach that P16:

i) has a molecular size of p16;

ii) is a truncated version of core protein;

iii) contains 16 amino acids of core;

iv) is recognized by antibody against the core protein;

v) accounts for 100% of the polypeptide produced in in vitro translation assays; and

vi) localizes in the nucleus.

The Xu 2001 reference teaches a polypeptide with distinctly different characteristics than those characteristics of P16. First, the P17 polypeptide taught by Xu et al. is of a different molecular size than P16, i.e., P17 rather than P16 (see Figure 1). Second, the Xu protein is taught to be a chimeric protein, comprising both core amino acid sequences and alternate reading frame sequences. The Xu protein is stated to be produced as a result of ribosomal frameshifting. Therefore, in contrast to P16, P17 it is not a truncated version of the core protein. Third, the Xu P17 polypeptide is taught to contain only about 10 or 11 amino acids of the core protein covalently linked to about 150 amino acids encoded in the +1 alternate reading frame (see Figure 3 and page 3844, column 2). Therefore, P17 has a different amino acid sequence than P16, which is taught by Lo to contain at least 16 amino acids of the core protein. Thus, P16 contains amino acids of the core protein that are not present in P17, i.e., core amino acids 12 to 16. Fourth, the P17 polypeptide is expressed in the cytoplasm. Four of the authors of the Xu 2001 paper authored a paper which teaches that P17 (F protein) is expressed in the cytoplasm (see Xu 2003 "Hepatitis C Virus F Protein is a Short-Lived Protein Associated with the Endoplasmic Reticulum" Journal of Virology 77:1578; attached as Appendix A, e.g., at p. 1580), whereas P16 was taught by Lo to be expressed in the nucleus. Roussel et al (Characterization of the expression of the hepatitis C virus F protein" Journal of General Virology, 2003, 84, 1751-1759;

attached as Appendix B) also report that P17 (F-protein) localizes to the cytoplasm (Figure 6, page 1756). Finally, the P17 polypeptide of Xu et al. 2001 is expressed as about 30% of in vitro product in a reticulocyte lysate assay (see Fig. 2, lane B1). On page 3846 Xu et al., EMBO J, 2001 state that the efficiency of ribosomal frameshifting is "~30% in vitro." This is in contrast to the finding that P16 is expressed as 100% of the product made in a reticulocyte lysate assay by the same laboratory and published in Lo B1.

Thus, there are distinct differences between the P16 polypeptide of Lo (B1 and B2) and the P17 (F protein) polypeptide taught by Xu et al. In order to establish inherency "the extrinsic evidence must make clear that the missing descriptive matter is ***necessarily*** present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill (emphasis added)." Harmon. R. L. "Patents in the Federal Circuit (6th Edition, Bureau of National Affairs, Inc. 2003). The Xu reference fails to establish that P16 and P17 are necessarily the same and, therefore, the prior art of record fails to teach or suggest alternate reading frame polypeptides as presently claimed.

In addition, even if P16 were an alternate reading frame protein, which Applicants deny has been established, one faced with the problem of improving HCV diagnostics at the time the invention was made would not have recognized it as such and would not have known that polypeptides encoded in their entirety or in part in the alternate reading frames of HCV or antibodies that recognize them could be used to diagnose HCV infection. The Federal Circuit has made it clear that something unknown to one of ordinary skill in the art cannot be used as the basis for making an obviousness rejection. "Obviousness cannot be predicated on what is unknown." In re Spormann, (CCPA 1966) 363 F.2d 444,448.

Moreover, the pending claims are directed to ***methods of diagnosing HCV infection***. The Lo B1 reference fails to teach or suggest methods of diagnosing HCV infection comprising

detecting the presence or absence of P16 or an antibody reactive therewith. The reference does not teach that P16, regardless of whether or not it is an alternate reading frame polypeptide, is expressed in during the course of HCV infection. ***All of the data in the reference was generated using in vitro translation experiments***. In addition, the reference teaches that P16 is only detected in ***one isolate*** tested, the HCV-1 isolate, which has a Lys-9 residue. A second closely related isolate, RH, was tested and it ***did not*** yield P16. Lo B1 considered expression of P16 to be dependent on the sequence of the HCV-1 isolate and they identified a highly unusual feature of the HCV-1 sequence—the Lys-9 codon, as a key contributor to P16 production. The limited expression of P16 taught in the reference ***teaches away*** from the use of P16 as a diagnostic.

Similarly, the Lo B2 reference fails to teach or suggest methods of diagnosing HCV infection comprising detecting the presence or absence of an alternate reading frame polypeptide or antibodies reactive therewith. The reference looks at expression of P16 from artificial constructs and teaches that P16 is expressed from these constructs in *E. coli* and CV1 cells. However, expression of P16 is taught to be enhanced ***in the absence*** of the E1 envelope protein. In the case of infection with HCV, the E1 envelope protein is present. The reference does not examine the expression of P16 in the course of HCV infection and there is no indication in the reference that P16 is made during infection.

Prior to Applicants invention, ***i) no one had identified alternate reading frame polypeptides having an amino acid sequence that differed from core, ii) no one had shown that such polypeptides were produced during an infection in a human subject, and iii) no one had shown that such polypeptides were immunogenic in a human subject.*** Absent Applicants teachings, there was no motivation present in the art to diagnose HCV infection by detecting the presence or absence of a polypeptide comprising an amino acid sequence encoded by an HCV alternate reading frame or antibodies reactive therewith. In fact, the Xu 2001 reference, cited by

the Examiner and filed after Applicants filing date, clearly states that based on the earlier work of others (including Lo B1 and Lo B2) whether the P16 or the F protein could be synthesized during natural HCV infection in patients was "***unclear***" (see Xu 2001, page 3844, column 1, paragraph 2). In contrast to the teachings of the prior art, Applicants have shown that alternate reading frame polypeptides are produced during infection and that they are immunogenic. Applicants provide a working example in which alternate reading frame polypeptides were synthesized and sera from patients with HCV were tested for their reactivity with the polypeptides. These data show that HCV patient sera contained antibodies reactive with alternate reading frame polypeptides.

Moreover, at the time the invention was made there was no reasonable expectation of success that HCV could be diagnosed using P16 or antibodies reacting therewith. There was no evidence that P16 had any epitopes that differed from the epitopes present in the core protein. In fact, the only antibodies reported by Lo B1 and Lo B2 to react with P16 were anti-core antibodies, not antibodies to epitopes encoded in an alternate reading frame. In addition, Lo B1 teaches that Lys-9 was critical for P16 expression (see page 127, column 1, paragraph 2) and, given that HCV-1 is virtually the only isolate with Lys-9, Lo B1 teaches that P16 is expressed by only one isolate. If Lys-9 were critical for P16 synthesis as concluded by the authors of Lo B1, HCV would not be expected to produce P16 during natural infections in humans except infections caused by HCV-1. In addition, Lo B2 teaches that P16 expression from HCV-1 was *decreased* when the E1 envelope protein was present in the construct. Given that E1 is present in normal infection, this result implies that P16 might be an in vitro artifact. Therefore, absent Applicant's teachings, one of ordinary skill in the art would not have had a reasonable expectation of success in using the claimed methods to diagnose HCV infection.

Accordingly, the claims are not obvious in view of the art of record and it is respectfully requested that this rejection be reconsidered and withdrawn.

Rejection of Claims 38-40, 42-44, 46, and 47 Under 35 U.S.C. 112, second paragraph.

The Examiner contends that claim 38 is indefinite in reciting "comprising an amino acid sequence encoded by a reading frame corresponding to the reading frame of SEQ ID NO:1." It is the Examiner's position that it is not clear how much amino acid sequence or what amino acid sequence encoded by the reading frame of SEQ ID NO:1 is required at minimum. This rejection is believed to have been obviated by the amendment to claim 38 to change the claim dependency. Claim 38 depends from claim 53 or 54. Each of these claims depend from claim 52 which requires that the polypeptide comprise an immunogenic amino acid sequence of an HCV alternate reading frame polypeptide or an amino acid sequence of an HCV alternate reading frame polypeptide that is immunoreactive with an antibody that specifically binds to an HCV alternate reading frame polypeptide. Accordingly, the alternate reading frame portion of the polypeptide must be capable of inducing an immune response or immunoreacting with an anti-alternate reading frame polypeptide antibody.

Claim 39 has been rejected as being indefinite because "it is not clear what 'at least about 8 amino acids to at least about 100 amino acids in length' is intended to mean." This rejection is believed to have been obviated by the amendment to the claim to clarify that the amino acid sequence is at least about 8 amino acids in length. Similarly, claim 40 has been amended to clarify the intended length of the amino acid sequence.

Claims 43 has been rejected as "it is not clear if the intended comparison of the comprised "amino acid sequence" is intended to be made over the entire length of SEQ ID NO:2." This rejection is believed to have been obviated by the amendment to claim 43 to

indicate that the comparison is intended to be made over a length of at least about 10 amino acids.

Claim 47 has been rejected as being indefinite because it recites SEQ ID NO:7 and SEQ ID NO:8. This rejection is believed to have been obviated by the amendment to claim 47 deleting the reference to these sequences.

Rejection of claims 29, 36, 31, 38-44, and 46-49 Under 35 USC § 112, first paragraph.

The Pending Claims are Enabled

Claims 29, 36, 31, 38-44, and 46-49 have been rejected Under 35 USC § 112, first paragraph as not being enabled by the specification. Claims 1, 14, 24-26, 28-31, 36 and 37 have been canceled. This rejection is respectfully traversed to the extent that it may be applied to any of the presently pending claims.

The Examiner states that "[t]he specification teaches, in Examples 1 and 2, that certain polypeptides derived from an HCV +1 reading frame detect antibodies that are present in the body fluid of subjects infected with HCV." The Examiner continues, "[w]hile the specification teaches that one can use such polypeptides to raise antibodies that may subsequently be used to detect polypeptides in tissue of body fluids of infected subjects (pages 20-25), the specification does not provide results of such assays that would serve to demonstrate that such polypeptides are actually circulating or present in the body fluids of infected subjects, or that antibodies raised against the disclosed polypeptides actually detect HCV +1 reading frame polypeptides in the body fluids or tissues of infected subjects." The Examiner relies on the fact that other groups teach that alternate reading frame polypeptides are only expressed in some patients and that a

role for the polypeptides in the HCV life cycle are not understood (citing to Varaklioti et al., The Journal of Biological Chemistry 20:17713-17721, 2002) and states that "lacking direct evidence that an HCV+1 reading frame polypeptide is present in the body fluid or tissue of an HCV infected subject, the specification cannot be said to enable one of skill in the art to practice the invention."

The pending claims are directed to detecting: i) a polypeptide comprising an immunogenic amino acid sequence of an HCV alternate reading frame polypeptide, ii) a polypeptide comprising an amino acid sequence of an HCV alternate reading frame polypeptide that is immunoreactive with an antibody that specifically binds to an HCV alternate reading frame polypeptide, and iii) an antibody that specifically binds to an HCV alternate reading frame polypeptide. Applicants point out that the data presented in the instant application, which shows that alternate reading frame polypeptides elicit immune responses in patients, indicates that the immunogenic alternate reading frame polypeptides are expressed in patients and, therefore, that such polypeptides are present in patient's cells and/or body fluids. Applicants point out that the development of an antibody response to a polypeptide is the standard by which the skilled artisan determines whether polypeptides are expressed in patients and that, given the immunological response data presented by Applicants, one of ordinary skill in the art would understand that antibodies immunoreactive with alternate reading frame polypeptides could be used to detect those polypeptides. As acknowledged by the Examiner, exemplary detection procedures are taught in Applicants specification. In addition, methods for detecting expressed HCV polypeptides were known to those of ordinary skill in the art at the time the invention was made. For example, Applicants provide a copy of an article by Walker et al. (1998. "Detection and Localization by In Situ Molecular Biology Techniques and Immunohistochemistry of Hepatitis C Virus in Livers of Chronically Infected Patients" Journal of Histochemistry and Cytochemistry.

46:653; attached as Appendix C). This reference was published prior to Applicants priority date and demonstrates detection of HCV proteins in patients' cells using antibodies (in this case labeled with immunogold). This reference teaches that standard immunohistochemistry can be used to detect expressed HCV polypeptides in cells and/or body fluids of patients.

Applicants also wish to make the following remarks of record with respect to the Varaklioti et al. 2002 reference cited by the Examiner. The Varaklioti et al. 2002 reference fails to detect expression of the ARFP/F/core +1 protein in all isolates (using *in vitro* expression assays. the protein was detected in HCV-1 and was not detected in the HCV-1a (H) isolate), apparently leading the Examiner to question the significance of expression of the protein. First, two authors of the Varaklioti reference cited by the Examiner have subsequently published a paper in which they show that both HCV-1 and HCV-1a (H) efficiently express the core +1 protein in infected cells (see Vassilaki and Mavromara. 2003. J. Biol. Chem. 278:40503; attached as Appendix D). Second, these authors also show that the predominant form of ARFP/F/core+1 protein produced *in vivo* in transfected cells may be smaller than the 16/17-kDa product synthesized in *in vitro* systems. Thus, both the 16-kDa and the 17kDa products may only expressed in HCV-1 and/or may be *in vitro* artifacts. Accordingly, studies which only look for presence of the 16kDa Lo protein and/or the 17kDa F protein may not provide an accurate indication of the presence of HCV alternate reading frame polypeptides. According to Vassilaki, and Mavromara, the peptides synthesized in vivo that contain epitopes encoded in the +1 ARF may be smaller than the peptides described by Lo and Xu. The Vassilaki and Mavromara reference also teaches that "the ARFP/F/core+1 protein may play a critical role in controlling the life cycle of the virus" (see page 40512, column 2, first full paragraph). Thus, although the exact role of alternate reading frame polypeptides may not yet be known, this does not constitute evidence of a lack of enablement of the claimed invention. Moreover, it is clear that the art now

acknowledges that antibodies that recognize alternate reading frame polypeptides are detectable in the sera of many infected patients, thus indicating that the alternate reading frame proteins are widely expressed, and are potentially important in the life cycle of the virus.

The Pending Claims Satisfy the Written Description Requirement

Claims 29, 36, 31, 38-44, and 46-49 have been rejected under 35 U.S.C. 112, first paragraph. It is the Examiner's position that Applicants have "not described the detection of the genus of HCV +1 polypeptides encompassed by the claims in such a way as to reasonably convey to one skilled in the art that the inventors had possession of a sufficient number of such polypeptides as to represent possession of the invention as claimed." This rejection is respectfully traversed to the extent that it may be applied to any of the presently pending claims.

It is Applicants' position that HCV alternate reading frame polypeptides and their methods of detection in diagnosis of HCV are adequately described.

In determining whether the Written Description requirement is met, the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, 'Written Description' Requirement" published in the Federal Register on January 5, 2001 state that the Examiner should:

> compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention. Such a review is conducted from the standpoint of one of skill in the art at the time the application was filed (citing to Wang Labs v. Toshiba Corp., (Fed. Cir. 1993) 993 F.2d 858, 865). . . . Information which is well known in the art need not be described in detail in the specification. (citing to Hybritech, Inc. v. Monoclonal Antibodies, Inc., (Fed. Cir. 1986) 802 F.2d 1367, 1379-1380).
>
> Page 1105.

At page 1106, the Guidelines further state that "[t]he description need only describe in detail that which is new or not conventional (citing to Hybritech, Inc. v. Monoclonal Antibodies, Inc., (Fed. Cir. 1986) 802 F.2d 1367, 1379-1380).

The alternate reading frame polypeptides presently being claimed must comprise an immunogenic amino acid sequence of an HCV alternate reading frame polypeptide or an amino acid sequence of an HCV alternate reading frame polypeptide that is immunoreactive with an antibody that specifically binds to an HCV alternate reading frame polypeptide. Applicants describe a genus of alternate reading frame polypeptides expressed by HCV nucleic acid molecules translated in alternate reading frames. Applicants teach that alternate reading frame polypeptides comprise epitopes that are translated from an HCV nucleic acid molecule, but rather than being read in the standard open reading frame, are translated from a reading frame which is +1 or +2 to the standard HCV open reading frame. Applicants teach how one of skill in the art could take any HCV nucleic acid sequence and shift it into an alternate reading frame to obtain the amino acid sequence of an alternate reading frame polypeptide, e.g., by using the an alternate reading frame of the HCV isolate having GenBank accession number AF011751 as a reference sequence (see, e.g., page 5 of the specification). A portion of the AF011751 nucleic acid sequence encoding an exemplary alternate reading frame polypeptide was provided as an example in Applicants specification. Given Applicants teachings, one of ordinary skill in the art could determine the nucleotide sequence encoding an alternate reading frame polypeptide by simply shifting the reading frame +1 or +2 to the standard ORF and, using the generic code, obtain the amino acid sequence of an alternate reading frame polypeptide sequence.

Numerous HCV nucleic acid molecules were well known and publicly available in the art at the time the application was filed. As set forth above, according to the Written Description Guidelines, known conventional information such as known HCV nucleic acid sequences need

not have been described in Applicants specification (see, e.g., Written Description Guidelines pages 1105 and 1106). Applicants submit that the exemplary known AF011751 nucleic acid sequence provided in the specification was sufficient to describe the genus of HCV nucleotide sequences. In addition, HCV nucleic acid sequences are all structurally related. Although there may be some variability among HCV nucleotide sequences, all such sequences are genetic information for HCV and not for other viruses and they comprise common features possessed by all HCV nucleic acid molecules as distinguished from other viruses. Moreover, Applicants note that USSN 60/089138, incorporated by reference into the instant application and to which the instant application claims priority, contains examples of additional nucleic acid sequences encoding alternate reading frame polypeptides.

In addition, Applicants provided examples of exemplary alternate reading frame polypeptides based on the nucleotide sequence of exemplary published HCV isolates AF011751, D17763, D10988, D14853, D00944, D63822, Y1604, and D50482 (see Table 1). Applicants developed a consensus (majority) alternate reading frame polypeptide sequence based on homology observed among alternate reading frame polypeptide sequences based on alternate reading frame translation of known HCV nucleic acid sequences (shown in Table 1). Applicants further demonstrated that such alternate reading frame polypeptides are expressed in the cells/fluids of patients with various strains of HCV by demonstrating that antibodies reactive with the consensus peptide were detected in such patients.

Given the description in the specification, one of ordinary skill in the art would have known that Applicants were in possession of the claimed invention. Armed with the knowledge of publicly available HCV nucleic acid sequences, the genetic code, and the benefit of Applicants teachings, one of ordinary skill in the art would have immediately understood that Applicants were in possession of at least hundreds of examples of alternate reading frame

polypeptides. Moreover, based on the fact that antibodies to a consensus alternate reading frame polypeptide were detected in HCV patients, one of ordinary skill in the art would have understood that Applicants were in possession diagnostic methods for detection of a genus of polypeptides or antibodies reactive with such polypeptides.

Applicants further point out that an appropriate claim scope is necessary to adequately protect Applicants' invention from those who could make a minor change to an HCV nucleic acid sequence or HCV alternate reading frame polypeptide amino acid sequence based on Applicants' broad teachings to avoid infringement while exploiting the benefits of Applicants' invention. To deny a claim of appropriate scope would serve to carve a pathway around the claims requiring no inventive contribution.

Applicants further note that the Written Description Guidelines at page 1109 require that the examiner present "***evidence or reasoning*** to explain why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims." This the Examiner has not done.

As the pending claims are enabled and adequately described, Applicants respectfully request that the rejection of claims 29, 36, 31, 38-44, and 46-49 as it may be applied to any of the pending claims under 35 USC § 112, first paragraph be reconsidered and withdrawn.

CONCLUSION

If a telephone conversation with applicant's agent would expedite the prosecution of the above-identified application, the examiner is urged to call applicant's agent at (617) 227-7400.

Respectfully submitted,

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